HemaSphere

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(S194) SEQUENTIAL ADMINISTRATION OF BISPECIFIC ANTIBODIES AND ANTI-BCMA CAR-T CELL THERAPY IN RELAPSED/ REFRACTORY MULTIPLE MYELOMA IS ASSOCIATED WITH EXPANSION OF CD8 EFFECTOR CLONES AND HIGH RESPONSE RATES

Topic: 13. Myeloma and other monoclonal gammopathies - Biology & translational research

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Background:

Optimal sequencing of T-cell engaging therapies (TCE) such as bispecific antibodies (BITEs) and chimeric antigen receptor (CAR-) T-cells remains a clinically relevant controversy in multiple myeloma (MM). Targeting B-cell maturation antigen (BCMA) with TCE in triple-class refractory (TCRRMM) or penta-refractory (PentaRRMM) MM has become an important option, leading to responses in most patients. Furthermore, bridging therapy (BT) may pave the way for successful CAR-T cell administration. In this study, we explore the effects of different BT regimens in preparation for CAR-T cell therapy.

Aims:

We characterized the clinical, immunological, and molecular features associated with different BT regimens to better understand their impact on T-cell repertoire dynamics and CAR-T expansion.

Methods:

We retrospectively included all 52 RRMM patients treated in our center with anti-BCMA CAR-T cell therapies (cilta-cel [n=18] or ide-cel [n=34]). Response was evaluated after BT and on Day 30 (D30) after CAR-T cell re-infusion according to IMWG criteria. CRS and ICANS were evaluated according to ASTCT guidelines. The T-cell compartment including CAR-T cells was characterized by flow cytometry. *In vitro* cytotoxicity assay of CAR-T cells was performed. Finally, the pre- and on-treatment TCR repertoire were profiled with paired longitudinal scRNA- and scVDJ-seq data.

Results:

Patients received either BITEs (teclistamab [n=5]; talquetamab [n=5]), chemotherapy (n=15), anti-CD38-based (n=19), or anti-SLAMF7-based (n=8) as BT. Patients who received BITEs had increased refractoriness and proportions of high-risk cytogenetics than other groups. Overall response rate (ORR) to BT was 57.7% and patients who responded to BT had significantly better PFS (P=0.035). Importantly, ORR to BITEs was significantly higher than for other BT regimens (100% vs. 47.6%, P=0.007). In all BT groups, there was effective *in vitro* cytotoxicity of CAR-T cells (BITE [n=6], chemotherapy [n=11], anti-CD38 [n=12], anti-SLAMF7 [n=6]). No significant differences between BT regimens were detected regarding side effects of subsequent CAR-T cell therapy. Immunophenotyping revealed differential CAR-T expansion dynamics in the BITE group, with early expansion on D7 and D14 after re-infusion of CD4+ CAR-T cells and delayed expansion of CD8+ CAR-T cells, which was also associated with CR on D30. Moreover, scTCR-seq analyses demonstrated increased clonality of the T-cell compartment at apheresis and on D30 after BITE therapy. Top clones were predominantly composed of cytotoxic CD8+ effector memory (EM) cells. At apheresis, T-cell exhaustion was highest in the BITE group, however proportions of exhausted cells did not differ after re-infusion between different BT regimens. On later time points, upon BT with BITEs,

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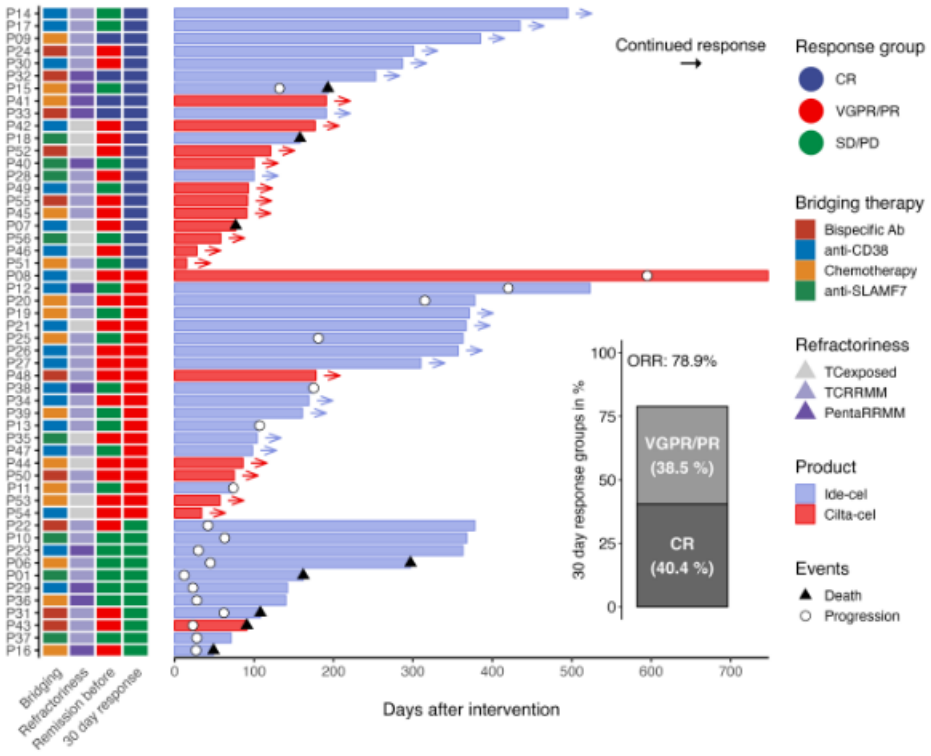
there was an elevated rate of CD8+ EM cells and cycling CD8+ cells in hyperexpanded clones, indicating increased capacity for long-term persistence.

Discussion:

Sequential administration of BITEs and CAR-T cell therapy achieved excellent responses even in TCRRMM and PentaRRMM patients. Here, we demonstrate that patients who received BITEs as BT for subsequent anti-BCMA CAR-T therapy showed favorable expansion dynamics with higher capacity for CAR-T long-term persistence. Finally, selection of CD8+ EM clones by BITE therapy prior to apheresis maintains T-cell fitness during CAR-T therapy. Our study highlights the importance and effects of different BT regimens in CAR-T cell therapy.



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